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CONTENTS

EDITORIAL

A BACKDOOR APPROACH

A PROPOSAL has been submitted to the Subcommittee on Internal Preparations of the *United States Pharmacopeia* which deserves comment since it is typical of the backdoor approach which only too often is used on the American scene rather than direct action. It has been suggested that the time-honored formula for paregoric (Camphorated Opium Tincture) be modified by the inclusion of calcium chloride. This addition is not for the purpose of improving the therapeutic efficiency of the preparation but is for the purpose of discouraging its misuse by narcotic addicts. The theory behind this suggestion is that the addict, when he attempts to boil down this weak preparation prior to its injection, will attain a hypertonic saline solution which will prove quite painful when injected subcutaneously. This might well prove to be the case but, when one studies this proposal from the standpoint of simple logic, it seems to be exceedingly farfetched. It is the function of the *United States Pharmacopeia* to recognize in monograph form those drugs and preparations which are considered by the Subcommittee on Scope to have outstanding therapeutic merit and, in addition, those substances used in various preparations and known as "pharmaceutic necessities". In developing the formula for any preparation, that formula is selected which makes the finished product the best possible for the therapeutic purpose intended. This is, has always been, and should continue to be the sole criterion in developing formulas for the Pharmacopeia.

Paregoric has been recognized officially for many years and it has been voted for inclusion in U. S. P. XVI. The therapeutic use for which it is intended is that of an intestinal sedative. By no stretch of the imagination can it be assumed that the addition of calcium chloride would improve this action.

Since this suggestion came from responsible sources in Washington, some members of the Subcommittee on Internal Preparations have attempted to determine just what new incompatibilities might arise were this modification made in this standard formula. It would

seem much more appropriate, however, to challenge the philosophy behind the suggestion and this surely is the position which we would take.

It is not the proper function of the Pharmacopeia to change its formulas in such a way as to make it inconvenient for drug addicts to misuse a standard exempt narcotic preparation. The federal law requires that all sales of paregoric be recorded and it is implied in the law that this preparation not be sold except for *bona fide* medicinal use. If, indeed, there is good evidence that this preparation is being widely misused to maintain addiction, then the proper remedy is to amend the regulations pertaining to its distribution and, if it is really necessary, to place it on a "prescription only" basis. Another approach and one much less drastic would be to make the sale of paregoric one restricted solely to the pharmacist himself and with more rigid controls.

We are sympathetic with the vast and continuing problem which the Narcotic Bureau faces in the control of drug addiction and the suppression of illicit narcotics. As we have said before, they deserve greater Congressional support in the matter of staff and finances than they presently get. On the other hand, we cannot endorse a suggestion—however well intentioned—which appears to us like "tilting at windmills". We also object to this proposal since it would subvert the purpose and proper function of the *United States Pharmacopeia*.

L. F. Tice.

AN EVALUATION OF THE ANTIBACTERIAL ACTIVITY AND RELATIVE STABILITY OF NOVOBIOCIN SODIUM IN SELECTED OINTMENT BASES *

By Edward Stempel,† Leo Greenberg, ‡ and Arnold Urdang †

NOVOBIOCIN sodium is the generic name of a recently introduced antibiotic salt commercially available from Merck Sharp & Dohme, Charles Pfizer & Co., and The Upjohn Company. The parent compound is obtained from either *Streptomyces spheroides* or *Streptomyces niveus*. Its antibacterial spectrum is closely related to penicillin and erythromycin. It is active primarily against gram-positive bacteria; is especially active against strains of *Micrococcus pyogenes* var. *aureus*, including strains resistant to other clinically effective antibiotics; and is bactericidal in effect (1).

Since novobiocin sodium is not, at this time, commercially available in an ointment dosage form, this study was undertaken to investigate the antibacterial activity and relative stability of this antibiotic in a number of selected ointment bases of various types.

Experimental

Materials.—Powdered Albamycin [1] (novobiocin sodium) was used. Other commercial preparations used were: Cold Cream (Lilly No. 25),[2] cholesterol,[3] Dermabase,[4] Ethofat 60/60,[5] Falba,[6] Hydrosorb,[7] Neobase,[8] Penassay seed and base agar,[9] Plastibase,[10] Plastibase

* Received from Brooklyn College of Pharmacy, Long Island University, Brooklyn, N. Y.

† Assistant Professor of Pharmacy.
‡ Assistant Professor of Microbiology.

[1] Generously contributed by Dr. J. J. Duggar, The UpJohn Co., Kalamazoo, Mich.

[2] Contributed by Eli Lilly & Co., Indianapolis, Ind.

[3] American Cholesterol Products, Inc., Milltown, N. J.

[4] Contributed by Marcelle Cosmetics, Inc., 1741 N. Western Ave., Chicago 47, Ill.

[5] Contributed by Armour Chemical Division, 1355 West 31st St., Chicago 9, Ill.

[6] Contributed by Pfaltz & Bauer, Inc., Empire State Building, N. Y., N. Y.

[7] Contributed by Abbott Laboratories, North Chicago, Ill.

[8] Contributed by Burroughs Wellcome & Co., Inc., 1 Scarsdale Rd., Tuckahoe 7, N. Y.

[9] Difco Laboratories, Detroit, Mich.

Hydrophilic,[10] polyethylene glycol 400 distearate,[11] polyethylene glycol 600 distearate,[11] polyethylene glycol 400 monostearate,[12] Polysorb,[13] Promulgen,[14] Qualatum,[15] Tween 60,[16] and Unibase.[17] Other materials used were of U. S. P. or N. F. quality, or their source is indicated subsequently.

Selection of Ointment Bases.—The ointment bases included in this study were divided into four types. These were: greasy or oleaginous bases; greasy absorption bases; washable absorption bases; and water-miscible bases which include oil-in-water emulsions (sometimes referred to as water-washable or hydrophilic bases) and water-soluble bases.

The bases are listed alphabetically in Table I according to the above classification. Those bases whose formulas are readily available in the U. S. P. bear that designation. Following are the formulas of those bases which are not commercially available:

Base G of Goldstein (2)	
Polyethylene glycol 400 monostearate	26
Polyethylene glycol 400	37
Polyethylene glycol 4000	37
Newman-Miller Base (3)	
Cholesterol	3
Tween 60	80
Stearyl alcohol	5
White wax	12
Polyethylene Glycol Distearate Base (4)	
Polyethylene glycol 400 distearate	5
Polyethylene glycol 600 distearate	10
Methylparaben	0.1
White petrolatum	85

[10] Contributed by E. R. Squibb & Sons, 745 Fifth Ave., N. Y. 22, N. Y.

[11] Contributed by Glyco Products Co., Inc., Empire State Building, N. Y., N. Y.

[12] Glyco Products Co., Inc., Empire State Building, N. Y., N. Y.

[13] Contributed by E. Fougera & Co., 75 Varick St., N. Y. 13, N. Y.

[14] Contributed by Robinson, Wagner Co., Inc., 110 East 42nd St., N. Y., N. Y.

[15] Contributed by Almay, Division of Schieffelin & Co., 28 Cooper Square, N. Y., N. Y.

[16] Contributed by Atlas Powder Co., Wilmington 99, Del.

[17] Contributed by Parke, Davis & Co., Detroit 32, Mich.

Hickman-Burlage-Lloyd Base (5)	
Cetyl alcohol	12
Stearyl alcohol	16
Ethofat 60/60	8
Propylene glycol	21
White petrolatum	43
Promulgen Base (6)	
Promulgen	30
White petrolatum	50
Light liquid petrolatum	20
Sodium Carboxymethylcellulose Base (7)	
CMC-M	6.0
Glycerin	12.5
Methylparaben	0.025
Propylparaben	0.015
Purified water	90.0

Selection of Novobiocin Sodium Concentration.—Four test ointments containing 10 mg. of novobiocin sodium per Gm. of ointment were prepared, and from these, ointments containing 0.1 and 1.0 mg. per Gm. were prepared. These ointments were tested against the test organism, and the antibacterial activity measured to determine the optimum concentration of antibiotic for experimental purposes. The results indicated that 1.0 mg. per Gm. was the optimum concentration for further use.

Absorption of Water in Absorption Bases.—Forty parts of each absorption base was combined with 20 parts of purified water (subsequently referred to as water). If a stable preparation did not ensue, then 40 parts of each base was combined with 10 parts of water. Table I indicates the ratio of base and water used.

Incorporation of the Novobiocin Sodium.—Ten milligrams of antibiotic was weighed on an analytical balance and incorporated into 9.990 Gm. of each base. The prepared ointments were transferred to emerald green Duraglas[18] ointment jars and stored at room temperature.

Evaluation of the Ointments by the Agar Cup-Plate Method.—Penassay seed and base agar were used as media. The inoculum was prepared from an 18-hour F. D. A. broth culture of *Micrococcus pyogenes* var. *aureus* 209P. The final concentration of organisms in broth at 18-hour incubation averaged 300 million per ml. regardless

[18] Owens-Illinois Glass Co., Toledo 1, Ohio.

of slight variations in the size of the initial inoculum. One milliliter of the 18-hour suspension was added to each 100 ml. of seed agar, previously melted and cooled to about 48°. Twenty milliliters of base agar was placed in each flat-bottomed petri dish and allowed to harden; after which 5 ml. of inoculum was poured evenly over the base agar surfaces, and permitted to harden in a refrigerator for at least one-half hour prior to use.

The antibacterial activity of each antibiotic ointment was determined by placing 3 samples of each and the control base in separate sterile porcelain-type Penicylinders [19] having an external diameter of 8 mm., and spacing these four uniformly on the test surface. The plates were incubated for 18 hours at 37°, and the diameters of the zones of inhibition were measured on a Quebec Colony Counter [20] using a millimeter rule under a high powered lens. The mean zone of inhibition produced by each ointment was compared with the control, and the results are shown in Table I.

TABLE I.

ANTIBACTERIAL ACTIVITY AND RELATIVE STABILITY OF NOVOBIOCIN SODIUM IN SELECTED OINTMENT BASES [a]

Bases	Mean Zone Diam. in mm. After One: Day	Week	Month	Approximate Mean % Loss in Activity After One: Week	Month
Greasy Bases:					
Petrolatum Rose Water Oint. U. S. P. XV	21.4	18.6	8.6	13[b]	60[b]
Cold Cream (Lilly No. 25)	17.4	8.0	4.0	54	71
Plastibase	17.4	12.0	14.6	33	16
White Petrolatum	41.4	13.0	9.0[c]	—	21
Greasy Absorption Bases:					
Falba	26.0	26.0	14.0	0	46
Falba:Water, 2:1[d]	28.0	26.0	26.0	7	7
Hydrosorb	29.4	29.0	22.0	2	21
Hydrosorb:Water, 2:1	12.6	14.6	22.0	—	—

[19] Fisher Penicylinder No. 7-907, Fisher Scientific Co., 633 Greenwich St., N. Y. C.

[20] American Optical Co., Buffalo, N. Y.

[a] Concentration is 1.0 mg. per Gm. of ointment.

[b] Mean zone diam. in mm. after one day taken as 100%.

[c] Infiltrated; presumably due to resistant colonies.

[d] Parts of base plus parts of water.

Bases	Mean Zone Diam. in mm. After one: Day	Week	Month	Approximate Mean % Loss in Activity After One: Week	Month
Hydrophilic Petrolatum U. S. P. XV	22.6	12.6	27.4	44	—
Hydrophilic Pet.: Water, 2:1	22.6	20.0	15.4	12	32
Plastibase Hydrophilic	31.4	30.0	26.0	4	17
Plastibase Hydrophil.:Water, 4:1	30.6	30.6	30.0	0	2
Polysorb	21.4	20.6	18.6	4	13
Polysorb:Water, 2:1	29.4	30.0	24.0	—	18
Qualatum	29.4	23.4	14.0	20	52
Qualatum:Water, 2:1	32.0	28.6	23.4	11	27
Wool Fat	26.0	24.0	20.6	8	22
Wool Fat:Water, 2:1	30.6	24.6	21.4	20	30
Washable Absorption Bases:					
Base G of Goldstein	36.6	31.0	24.0	15	34
Base G of Goldstein:Water, 4:1	47.4	26.6	22.0	44	54
Hickman-Burlage-Lloyd Base	26.0	28.0	26.0	—	0
H-B-L Base:Water, 2:1	34.6	25.4	20.6	27	40
Newman-Miller Base	20.0	17.0	9.0	15	55
Newman-Miller Base:Water 2:1	26.0	22.0	10.0	15	62
Promulgen Base	24.6	20.0	15.4	19	37
Promulgen Base:Water, 2:1	28.6	26.0	22.6	9	21
Water-Miscible Bases:					
Dermabase	32.6	31.0	28.0	5	14
Hydrophilic Ointment U. S. P. XV	36.0	33.4	30.6	7	15
Neobase	31.4	24.0	22.0	24	30
Polyethylene Glycol Distearate Base	22.6	20.6	17.4	9	23
Polyethylene Glycol Oint. U. S. P. XV	38.6	34.0	19.0	12	51
Sodium Carboxymethylcellulose Jelly	35.4	32.0	34±*	10	?
Unibase	34.0	32.0	27.0	6	21

* Leakage over top of Penicylinder; result uncertain.

Discussion

Of the greasy bases used as vehicles for novobiocin sodium, the product using Petrolatum Rose Water Ointment U. S. P. XV showed, at the end of one week, the greatest antibacterial activity, while the antibiotic was relatively stable. After one month's storage, the product containing Plastibase had the greatest antibacterial activity, while the antibiotic was most stable.

Of the greasy absorption bases used, the products containing Plastibase Hydrophilic-Water (4:1), Plastibase Hydrophilic, or Polysorb-Water (2:1) showed the greatest antibacterial activity at the one-week test period; moreover, the stability of the antibiotic in those bases was very good. The one-month study indicated efficient release and good stability of the antibiotic in either Plastibase Hydrophilic-Water (4:1) or Falba-Water (2:1). In general, those bases containing water showed greater release of the antibiotic than the corresponding anhydrous base, with the exception of Hydrosorb-Water (2:1). Paradoxically, Hydrosorb-Water (2:1) increased the rate of release of the antibiotic with time.

The washable absorption bases used showed good release of the antibiotic; however, the stability of the antibiotic in those bases was unfavorable. The product containing Goldstein's Base G-Water (4:1) was very effective, but the antibiotic was very unstable in the vehicle. The antibiotic was effective and stable in the Hickman-Burlage-Lloyd Base at the end of the test periods; therefore, that base can be considered the vehicle of choice among the washable absorption bases.

Hydrophilic Ointment U. S. P. XV appeared to be the base of choice among the water-miscible vehicles; at the end of one month, the product containing it showed a relatively good release of the antibiotic, and the antibiotic was rather stable. Polyethylene Glycol Ointment U. S. P. XV released the antibiotic to a large degree, but the antibiotic proved to be rather unstable.

As one might expect, the greasy bases did not release the antibiotic as readily as the other three types of vehicles. In addition, there was no correlation between the four types of bases with regard to the stability of the antibiotic.

Summary

1. The antibacterial activity and relative stability of novobiocin sodium in various ointment bases has been determined.

2. Because of the known advantages of the water-miscible bases, Hydrophilic Ointment U. S. P. XV is recommended for the extemporaneous incorporation of novobiocin sodium in ointments.

3. If a washable absorption base is desired by the physician, the Hickman-Burlage-Lloyd Base is efficient.

4. If a greasy absorption base is desired by the physician, Plastibase Hydrophilic-Water (4:1), Falba-Water (2:1), or Hydrosorb-Water (2:1) are acceptable.

5. Since the greasy bases containing novobiocin sodium showed the least antibacterial activity, the remaining three types of bases should be used when greater antibacterial activity is desired.

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TODAY'S PROBLEMS IN PHARMACEUTICAL ETHICS *

By John N. McDonnell, D.Sc.**

CHANGING times and customs modify opinion concerning what is right and what is wrong. This applies as well to one's relationship with one's fellow man. The bases for this relationship are established under the general term of "ethics."

Ethics and Morality

Man's ethics are closely bound with his morality. It is not easy to discuss the subject of ethics in relation to one's own morals and morality, and in the light of today's manners and customs, and of present day business. It is even more difficult to appraise ethics in terms of professional practice.

Throughout the Americas, new challenges to the ethics of the profession have developed. Some have come from the rapid advances in diagnosis and treatment of disease, some from the impact on life of the discovery of new and extremely potent therapeutic agents. Others have arisen from the changing economic approach to professional practice. Other new challenges have grown out of new economic standards and the strain of modern life. However, all bring with them renewed appreciation of the vital importance of ethics, especially in our profession of Pharmacy.

The Obligations of Pharmacy

The pharmacist knows that he must recognize his responsibilty in his dealings with the physician. He understands as well that because of his professional position, he must guarantee the highest calibre of service to the public. But today, the pharmacist discovers that he must also recognize his obligation to other pharmacists in practice. In addition, he owes a duty and responsibility to the pharmaceutical manufacturer.

Pharmacists are too ready to take for granted their obligation to professional ethics. They view it with as much unconcern as they blandly accept the apparent professionality of Pharmacy. They fail

* Presented before the Section on Pharmaceutical Economics and Management, Fourth Pan-American Congress of Pharmacy and Biochemistry, Hotel Mayflower, Washington, D.C., U. S. A., November 3rd-9th, 1957.

** Vice-President, Schering Corporation, Bloomfield, New Jersey, U. S. A.

to realize that in moments of stress these obligations must dictate their practice as well as limit their livelihood.

If the pharmacist observes these obligations at all times, it will insure his continued acceptance by the allied professions. It gains for him as well the respect of the public and of government. If he fails to live within the tenets of this responsibility or weakens his ethical approach to practice, he will lose his own professional respect, endanger his position and future, and as well jeopardize the position of the profession as a whole.

Economic and political pressures today threaten the inviolability of the ethics of the professions. As a consequence, organized Pharmacy is finding necessary the modernization and strengthening of its declared "principles." There is apparent need for expansion of Pharmacy's ethical structure to include economic and political principles, in addition to the professional.

The Meaning of Ethics

Let us first come to an understanding of what we mean by "ethics." Webster [1] explains the meaning of "ethics" to be the basis of morality. He defines it as the foundation for deciding as to what is right and what is wrong. He explains ethics as being the moral and social obligation which one owes to oneself, to one's fellow man, and to the community in general. In terms of rules of practice, he further defines "ethics" in its application to one's daily activities, to business, and to professional life. Thus the terms "business ethics," "social ethics" and "professional ethics" have evolved.

The Difference in Ethics

As interpreted today, business ethics leaves something to be desired when compared with morality based upon honesty, equity and "the golden rule."

[1] Webster's "Universal Unabridged Dictionary" (1936) defines "ethics" in the following terms: "ethics, n. (Gr. ta. ethika, ethics). 1. The science which treats of the nature and laws of the actions of intelligent beings, these actions being considered in relation to their moral qualities; the science which treats of the nature and grounds of moral obligation; the science of human duty. 2. The whole of the moral sciences; natural jurisprudence, including moral philosophy, international law, public or political law, civil law, and history, profane, civil, and political. 3. A particular system of principles and rules concerning duty, whether true or false; rules of practice in respect to a single class of human actions; as social *ethics;* newspaper *ethics.*"

The difference between the application of ethics to ordinary business and the application of ethics to Pharmacy lies in our professional status. We are bound by the much higher moral code of our profession, rather than merely by the morality of the market place.

The introduction of "professional" into the definition of "ethics" causes one to view the subject from a different aspect. For more than twenty centuries the professions have accepted the need for and the importance of firm statements of ethical principles established on a higher moral level. In Pharmacy and Medicine these have taken the form of "codes of ethics." [2]

The Ethics of Pharmacy

Regardless of era or national origin, pharmaceutical ethics customarily delineates the obligation and duty of the practicing pharmacist. This describes the full service which the community pharmacist must render to the public in the safe handling of drugs.

It recognizes his responsibility for upholding the standards in his profession. It insures his observance and application of all safeguards for the public. He is charged with guarding the confidence of his patrons. He must preserve and further their health and welfare. He is obligated to obey and defend the laws which pertain to his practice. In turn, he can demand only an honest remuneration.

He is expected as well to aid and inform, when necessary, members of the allied professions. He must dispense their prescriptions accurately and properly and observe the confidence of the physician. He is expected to enlarge his own knowledge of professional and scientific matters and to contribute to the body of knowledge of Pharmacy in general. He is expected at all times to be conscious of and proud of the heritage of his profession. These are basic precepts of professional practice.

Custom and Ethics

In the interests of the public health and welfare and in accord with the expectations of the allied professions, the dispensing pharmacist must do more than merely comply with Pharmacy's laws. There are other aspects of pharmaceutical ethics today which may or

[2] McDonnell, John N. "Do the Ethics of My Profession Apply to Me?" 78th Annual Meeting, Texas Pharmaceutical Association, Dallas, Texas, U. S. A., August 12, 1957.

may not be generally accepted. Their acceptance depends upon local custom. What may be "ethical practice" in one country may be viewed differently in another, in accordance with the latter's differing local conditions.

In some countries, the interrelationship of Medicine and Pharmacy is close and firm. There, the physician concentrates his professional efforts on diagnosis and prescribing. There too, the pharmacist is accorded complete responsibility for compounding and dispensing of all drugs. It is "unethical" for the latter to diagnose or "counter-prescribe."

Ethics and the Physician

In most countries, it is unethical for the pharmacist and the physician to engage in clandestine economic arrangements. In most others, the medical and pharmaceutical professions are independent financially and in practice. They are respectful of each other's prerogatives.

Again in some countries, it is still possible for physicians to gain profit from their own prescribing and even employ pharmacists for the dispensing of their own prescriptions. In the United States and Great Britain for instance, physicians still retain and to some small degree exercise a legal right to dispense some or all of their own medication, and in these countries legally or illegally, pharmacists in retaliation diagnose simple ailments and "counter-prescribe." In many countries, the pharmacist administers the drugs the doctor prescribes; in others, it is illegal for him to do so.

Ethics and the Patient

Exploitation of the patient by pharmacist and physician by secret arrangements, contractual arrangements and rebates, clandestine procedures or secret formulations is to be condemned.

Disparagement to the layman of the work and service of Pharmacy or of our allied professions is unethical. Degradation or calumny of physician, fellow pharmacist or pharmaceutical product is unethical. Any action which deliberately misleads the layman and harms other pharmacists and the prestige of the profession is equally to be condemned.

Recommendation or sale of a therapeutically valueless drug product, or of a nostrum knowingly to a patient in need of proper medical care, merely for the sake of profit, is a violation of ethics.

Pharmaceutical Colleagues

In his relations with his colleagues, the pharmacist must strive to accord to them the same courtesy, professional respect and recognition that he in turn expects and that is so markedly the rule within the medical profession. Regardless of his personal feelings toward another pharmacist, the pressure of competition in the market place, or the demands of an unthinking public, each pharmacist must be ready and willing to help or serve his colleagues in their time of need and to preserve their professional standing and reputations in the eyes of the allied professions and the public. The protection of public confidence in therapy and the prescription must be maintained. However, where such exists, he must expose corruption and dangerous incompetence, but only to the proper authorities. Claims by him for superiority in practice, and indulgence in promotional and marketing technics which derive special privilege or profit at the direct expense of his colleagues are to be condemned.

It is unethical for professional persons to advertise their professional services. When the price of a prescription is advertised, professional services are being advertised, and this is considered unethical in all professions.

Ethics and the Industry

There is an important aspect to the ethical relationship between pharmacist and pharmaceutical manufacturer which cannot be ignored. In the pharmacist's dispensing of drugs, "substitution" is unethical except when replacement is specifically approved by the prescriber, or without in his absence in the rare instance of emergency or where safety is in judgment. The prescriptionist must learn to view the manufacturer as a fellow pharmacist engaged in specialized, large scale practice, and governed by similar ethical principles. His rights and privileges must be observed as well or all Pharmacy will suffer.

The wholesale druggist and the pharmaceutical manufacturer are equally bound in practice and in business by pharmaceutical ethics. The manufacturer and the wholesaler must observe the same regard for the public's health and welfare. They must refrain from practices which unfairly attack and harm their competitors, or the retail or hospital pharmacists. After all, the pharmaceutical manufacturer today is an integral part of the profession of Pharmacy and as well professionally dedicated to the interests of public service. It is the

basic responsibility of the industry to serve the public and the profession honorably, honestly and faithfully, just as it is the duty of the prescriptionist. His code of ethics guarantees the manufacture of pure, standardized and effective pharmaceuticals. A manufacturer is forbidden to misrepresent claims for his preparations. He may not infringe upon the moral or legal rights of a competitor, interfere unfairly with his business, disparage him and his products, misappropriate his trademarks, property or products, or entice away his employees. He must not compete by unfair means through legal restriction, sanction or exclusion.

As well, he must recognize his responsibility to the prescription and hospital pharmacist as well as to the doctor, the patient and to government.

The Challenge of Today

Today's pressures tend to destroy and negate the influence of ethics. Life's tempo today, the economic battle for survival, and the moral breakdown of clashing ideologies attack the principles upon which professional practice and ethics are based.

Government gives to Pharmacy full powers for self-regulation by its own practitioners. This delegation of authority is unequalled, except in the instances of the other professions of Medicine, Dentistry and Nursing.

We must strengthen respect for professional ethics and insist within our group that ethics be observed in practice. Pharmacy must come to grips with the problem of dealing decisively with proven violators of ethics just as much as of law.

We must recognize our ethical responsibilities even at the cost of personal loss of income and profit. We must individually demonstrate the meaning of ethical practice and convince our fellow practitioners of its merit. Pharmacy may eventually have to force some into acceptance and punish others until their submission.

The influence of our professional ethics carries over into our more mundane commercial activities. We are professional men and women. Let us act and live as such.

STUDIES OF THE GENUS THYMUS

PART IV

Comparison of the Diagnostic Microscopical Characteristics of Thymus capitatus Hoffmagg. and Link and Thymus striatus Vahl.

By Ikram Hassan * and M. S. Dunn **

IN two papers previously published (3, 4), the authors made microscopical studies of the tissue elements of leaves, stem and flowering parts of Thymus vulgaris Linn., Thymus Serpyllum Linn., Thymus Chamaedrys Fries, and Thymus Herba-barona Loisel. The present work reports our findings of microscopical studies made on Thymus capitatus Hoffmagg. and Link and Thymus striatus Vahl.

Seven samples of both Thymus capitatus Hoffmagg. and Link, and Thymus striatus Vahl were studied from the following authoritative sources: Herbaria of the Philadelphia Academy of Natural Sciences, Botanical Garden of the University of Montreal, Harvard University, New York Botanical Garden, Munich Botanical Garden; Martindale Collection of the Philadelphia College of Pharmacy and Science; U. S. National Herbarium; and the Bailey Hortorium.

The material used in these studies although taken from herbarium sheet specimens collected or identified by recognized plant taxonomists was nevertheless compared for authenticity with the descriptions given by Bailey (1) and Engler and Prantl (2).

Method of Study

The method used in our work on Thymus capitatus Hoffmagg. and Link and T. striatus Vahl was the same as that employed in the case of T. Chamaedrys Fries and T. Herba-barona Loisel (3). Microscopical studies were made of the leaf, stem, calyx, and corolla.

An average palisade number count (Silverman and Dunn (5)) of T. capitatus Hoffmagg. and Link and T. striatus Vahl and a determination of the average number of leaf stomata (lower epidermis) per small central square unit of the Howard micrometer ruling were made in case of T. striatus Vahl.

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Summary

From the detailed mass of data our studies have provided, the facts outlined below seem to be noteworthy:

I. The comparison of the palisade number of T. capitatus and T. striatus based upon an average of 36 counts in case of T. capitatus and 40 counts in case of T. striatus, seems to be of some value in the separating of these species. The palisade number of T. capitatus was found to average 7.3, while that of T. striatus was 12.5.

II. The average number of stomata per small central square of the Howard reticule in the case of T. striatus was 10.0 based on 32 counts. The greatly-thickened walls of the cells of the lower epidermis made the count of the stomata per small central square unit of the Howard micrometer ruling too difficult to be practical in case of T. capitatus.

III. A comparison of other histological differences found in the two species is given below:

A. Floral Leaf

1. Thick lignified (tested with phloroglucin and HCl) hypodermal cells appearing as stone cells in the surface view (Fig. I, 1, 4C) below the upper epidermis were very prominent in all the

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FIGURE I.

Thymus Capitatus Hoffmagg. and Link.

1. Hypodermal stone cells of the leaf in surface view.

2. Three-celled glandular hairs of the leaf.

3. Transverse section of part of the leaf showing upper and lower palisade layers.

4. Transverse section of part of leaf showing hypodermal tissues (epidermis was so thin that it could be seen only in a few places.

5. Smooth-walled nonglandular hairs from the lower epidermis.

Thymus Striatus Vahl.

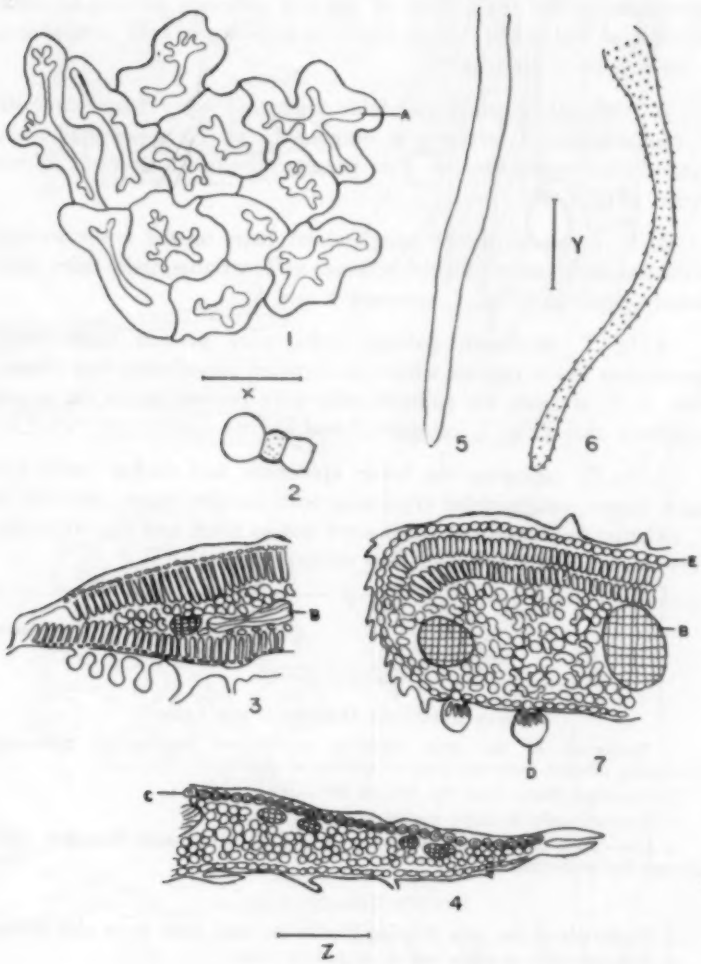
6. Papillose nonglandular hairs from the lower epidermis.

7. Transverse section of part of leaf showing absence of both hypodermal stone cells and lower palisade.

Drawings 3, 4, and 7 semidiagrammatic.

A. Lumen of the stone cell. B. Vein of the leaf. C. Hypodermis of the leaf. D. Multicellular glandular hair. E. Epidermis.

All drawings made with the aid of camera lucida. Scale X-34 microns for drawings 1 and 2. Scale Y-150 microns for drawings, 3, 5, 6, and 7; and scale Z-300 microns for drawing 4.


A
1
X
2
Y
5
6
B
3
E
B
D
7
C
4
Z

specimens studied of T. capitatus. The region of these hypodermal cells extended irregularly from the midrib toward the margins over approximately the basal ⅔rds of the leaf although varying to some degree from leaf to leaf. Such thickened hypodermal cells were absent in the case of T. striatus.

2. Although 2-celled glandular trichomes were found in both T. capitatus and T. striatus as outgrowths of the upper epidermis, 3-celled glandular trichomes were present only in T. capitatus in this region (Fig. I, 2).

3. In T. capitatus, the nonglandular hairs on the lower surface of the leaf were smooth-walled, whereas in T. striatus, these hairs were densely papillose (Fig. I, compare 5 and 6).

4. In T. capitatus, palisade cells were present under both epidermises in the regions where the lignified hypodermis was absent, while in T. striatus, the palisade cells were present under the upper epidermis only (Fig. I, compare 3 and 7).

5. In T. capitatus, the lower epidermis had thicker walls and much larger nonglandular trichomes with swollen bases, whereas in T. striatus, the epidermal walls were not so thick and the trichomes were much smaller and possessed narrower bases.

FIGURE II.

THYMUS CAPITATUS HOFFMAGG. AND LINK.

1. Epidermis of the stem showing absence of papilla-like trichomes (trichomes present were too long to qualify as papillae).

2. Lignified fibers from the ribs of the calyx.

3. Palisade cells in calyx region in surface view.

4. One-celled trichome of the inner surface of corolla with shrunken walls and peg-like projections.

THYMUS STRIATUS VAHL.

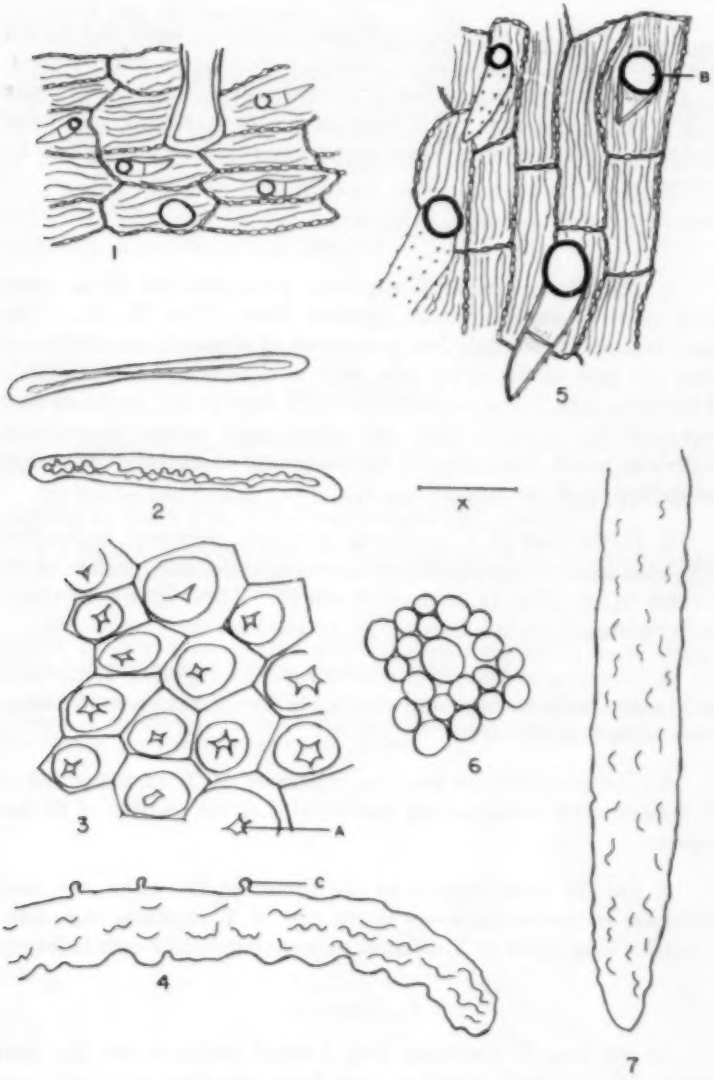
5. Epidermis of the stem showing papilla-like hair, other hairs also shown.

6. Palisade cells in calyx region in surface view.

7. One-celled trichome of the inner surface of corolla with shrunken walls.

A. Lumen of the unlignified cell. B. Papilla-like hair of stem. C. Peg-like projection.

All drawings made with the aid of camera lucida. Scale X-34 microns for all drawings.


1
B
5
2
X
3
A
6
C
4
7

B. Stem

In case of T. capitatus, papilla-like trichomes were absent; 2-4 celled uniseriate nonglandular, smooth-walled hairs were present. T. striatus showed papilla-like trichomes and 1-5 celled uniseriate nonglandular trichomes. All hairs of the stem surface mentioned above in T. striatus were found to possess papillose walls (Fig. II, compare 1 and 5).

C. Calyx

1. The rib regions of T. capitatus were protected by an outer layer of thick-walled, heavily lignified fibers (Fig. II, 2). This layer became increasingly less prominent as it passed outward away from the base of the calyx tube until at approximately the middle of the calyx tube, it was reduced to a single fiber or so. In the divided region of the calyx the fiber zone often again became increasingly noticeable in the main ribs. The fibers were absent from the calyx rib regions in T. striatus.

2. In the case of T. capitatus, especially thickened, unlignified cells lying under the epidermis were present in the outer surface of the divided region (Fig. II, compare 3 and 6). These cells were absent in T. striatus.

3. The nonglandular trichomes in the calyx region of T. capitatus had smooth walls throughout, whereas in T. striatus these trichomes were densely papillose.

4. The nonglandular marginal trichomes of T. capitatus and of T. striatus were 1-4 cells long and situated at the margins of all five sepals.

5. On the inner surface of the throat of the calyx, the nonglandular uniseriate trichomes in the case of T. capitatus were from 1-4 celled long, while in T. striatus, they ranged up to 7 cells in length.

D. Corolla

In the case T. capitatus, long 1-celled trichomes on the inner surface of the corolla tube had irregularly shrunken walls with peg-like projections (Fig. II, 4C), occurring here and there, whereas in

the case of T. striatus although such hairs were present, they were devoid of peg-like projections (Fig. II, *7*).

On the basis of structural deviations mentioned above and summarized below, it seems logical to the authors to accord T. capitatus Hoffmagg. and Link generic or subgeneric rank as indicated in Engler and Prantl under the title Corydothymus: 1. Presence of stone cells in the leaf. 2. Presence of lignified fiber zones in the calyx. 3. Presence of thickened, although unlignified palisade cells in the calyx. 4. Presence of peg-like projections on the walls of 1-celled trichomes of corolla (inner surface).

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THERAPY OF 353 CASES OF LYMPHOCYTIC LEUKEMIA WITH FOLIC ACID ANTAGONISTS

By John R. Sampey *

THE folic acid antagonists, aminopterin, amethopterin, amino-anfol and teropterin, have not fulfilled their early promise in the management of lymphocytic leukemia. The present study of 44 clinical reports since 1949 shows a remission rate of only 51% in 353 cases, and all but four of the investigations were carried out before 1954. A much higher remission rate has been observed in other chemotherapeutic agents on lymphoid and myeloid leukemias.[1]

Only 17 cases of chronic lymphocytic leukemia have been treated with FAA in this study, but the rate of remission (10 out of 17) is slightly better than that in the acute form (169 out of 333). However, Wintrobe, et al., state that FAA therapy is contraindicated in chronic cases, and Berman, et al., describe bad toxic reactions. A more detailed evaluation of folic acid antagonists therapy of lymphocytic leukemia is given in Table II.

The original literature was made available by the National Library of Medicine, and the libraries of Furman University and the Greenville General Hospital.

TABLE I

FAA Therapy of Lymphocytic Leukemia

No. of Refs.	No. of Cases	Acute Cases	Chronic Cases	Remissions	No. of Refs. Not Stating Rems.	Remission Rate
44	353	333	17	179	4	51%

* Furman University, Greenville, South Carolina.

[1] Sampey, J. R., *J. So. Car. Med. Assoc. 53*, 202 (1957); *54*, 53 (1958).

TABLE II

MANAGEMENT OF LYMPHOCYTIC LEUKEMIA WITH FAA

Cases	Acute	Chronic	Remissions	Comments on Therapy	References
43	43	—	16	Aminopterin. 8 complete, 5 partial remissions in 19 children. 3 complete rem. in 24 adults.	Stickney 1952
38	38	—	20	10 good remissions, 10 fair.	Wilson 1951
25	25	—	9	Good remissions of 21 to 240 days.	Wilson 1950
20	20	—	8	Good but brief rem. with cortisone and ACTH also.	Kelty 1953
19	19	—	9	6 of 12 children, 3 of 7 adults had fair rem.	Meyer 1949
15	15	—	12	9 complete, 3 partial rem. in children.	Wolman 1952
15	15	—	6	7 acute had 1 rem., 8 subacute had 5 rem. to 25 mos.	Dameshek 1950
14	14	—	10	Good remissions to 10 mos.	Mickle 1951
12	12	—	7	6 partial rem. to 3 mos., 1 to 14 mos.	Cottle 1952
12	12	—	12	Fair remissions.	Mendonca 1951
11	11	—	6	Complete remissions.	Soto 1952
10	10	—	5	Clin. and hemat. rem. of 2 to 8½ mos.	Dameshek 1949
10	10	—	6	3 good rem., 3 fair in subacute. Ineffective in acute fulminating type.	Hendricks 1951
10	10	—	1	Only 1 important remission.	Maurice 1952(1)
10	7	3	1	Only 1 brief remission.	Mendonca 1950
9	9	—	5	Hematologic improvement with antibiotics and blood transfusions also.	Smith 1950

Cases	Acute	Chronic	Remissions	Comments on Therapy	References
8	8	—	6	Spleen, lymph nodes and bone marrow almost normal in children for months.	Begemann 1954
8	8	—	6	Good remissions in children.	Begemann 1952
8	8	—	6	Clinical and hemat. rem. for months.	Haverkamp 1950
7	7	—	1	Only 1 significant rem. Bad toxic effects.	Dacie 1951
6	6	—	1	Good clinical remission only.	Meyer 1950
5	5	—	1	Brief remission, but end hastened in 2 cases.	Soto 1950
4	—	4	3	Objective clinical and hematologic remissions.	Wright 1950
4	4	—	4	3 complete, 1 partial rem.	McCall 1950
4	—	4	3	Brief but good remissions.	Wright 1951-52
4	—	4	2	Hemat. rem. only. Bad toxic reaction.	Berman 1949
3	3	—	3	1 complete, 2 partial rem.	Wilkinson 1953
3	—	—	—	No remissions.	Burchenal 1951
2	2	—	2	Brief remissions.	Gouttas 1952
2	2	—	1	FAA + TEM. Good rem. FAA + x-rays had no effect.	Marmont 1953
2	—	2	2	Fair remissions.	Pricolo 1949
2	2	—	—	Results do not justify use of FAA.	Maness 1949
2	2	—	—	No remission. 1 case died of hemorrhage in 1 mo.	Ruggeri 1952
1	1	—	1	Excellent clin. rem. after 14 weeks.	Alexander 1950
1	1	—	1	Remission for 6 months.	Gerwelowa 1952
1	1	—	1	5 year survival, 3 rem. of 11 to 16 mos.	Hays 1956

Cases	Acute	Chronic	Remissions	Comments on Therapy	References
1	1	—	1	Complete clin. and hemat. remission.	Jersild 1951
1	1	—	—	Failed to affect clin, or blood picture.	Khosla 1953
1	1	—	1	Survival for 20 months. X-rays, transfusions.	Moody 1950
—	—	—	—	Effective when ACTH, cortisone resistance develops.	Eliel 1954
—	—	—	—	Longer rem. following ACTH, cortisone.	Maurice 1952(2)
—	—	—	—	Good rem. in lymphoid and myeloid leukemias.	Sacks 1952
—	—	—	—	Good rem. in acute, contraindicated in chronic.	Wintrobe 1954

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SELECTED ABSTRACTS

The Comparative Effects of Hydrocortisone and Coal Tar in Atopic Dermatitis. Clyman, S. G. *Postgrad. Med. 21:309* (1957). A comparative study of the effects of hydrocortisone, coal tar extract, and a combination of the two in the treatment of atopic dermatitis was completed in 23 patients. The symmetrical comparison study was performed by applying each of the three preparations on a specific involved area of the body of the patient. The patients were carefully instructed not to change the order of application nor to mix or superimpose the creams. All three preparations were provided in a vanishing cream base. One contained 0.5 per cent hydrocortisone free alcohol, the second 5 per cent coal tar extract, and the third a combination of these in the same strengths.

The results were evaluated after one week and again after two weeks of application. It was found that the hydrocortisone-coal tar extract combination had an additive or possibly synergistic effect. In all but one case, marked clinical improvement was observed with the combination, and in no case was there total lack of improvement. In the one case of lichen simplex chronicus and in the two cases of nummular eczema, the superiority of the combination was very distinct. In cases in which pruritus accompanied the ezematous lesions, the alleviation was most prompt, most marked, and most lasting in the areas where the combination was used. In nine cases it was noted that improvement with hydrocortisone alone was superior to that with coal tar alone while in two cases the reverse was true.

No adverse reactions were observed in any area in which the combination cream was used. Two patients were observed to be sensitive to coal tar alone and one to hydrocortisone alone but neither showed sensitivity when the combination was employed.

The author suggested that the response to the combined treatment might be due to the anti-inflammatory action of hydrocortisone acting together with the keratoplastic action of coal tar. He also suggested that the results would warrant further investigation into whether or not the avoidance of refractoriness is a dependable feature of the combined therapy.

Solutions of Hydrocortisone and Prednisolone in Ophthalmology. Kreft, W. W. *Illinois Med. J. 112:*109 (1957). The treatment of 150 patients with a variety of ophthalmic conditions was accomplished by the use of solutions of hydrocortisone and of prednisolone in the alcohol form. Both solutions contained 0.2 per cent of the steroid and were colorless, sterile, buffered, and isotonic.

The author pointed out that these solutions have an advantage over suspensions in that they produce a minimum of discomfort and no disability. In contrast to ointments, they can be administered more easily by the patient and are, therefore, more likely to be effective. No case of dendritic ulcer was observed following the use of either solution.

The author indicated that only occasional complaints of mild stinging were voiced by the patients, following the instillation of these solutions. In no case was it necessary to discontinue the drops because of discomfort. Initial treatment consisted in the instillation of the drops every hour during waking hours. The period of treatment lasted from 1 week to 8 months.

Results of treatment were rated as good when symptoms were relieved in 24 hours and were eliminated within 7 days. Good results from treatment were obtained in 134 of 146 patients with the following conditions: allergic conjunctivitis, allergic dermatoconjunctivitis, vernal conjunctivitis, pingueculitis, phlyctenular keratoconjunctivitis, diffuse episcleritis, traumatic and postoperative iritis, and nongranulomatous iritis. The response was also good in a few cases of herpes zoster, marginal ulcer, superficial punctate keratitis, and recurrent corneal erosions.

Calcium and Phosphorus Metabolism as Affected by Ascorbic Acid. Leichsenring, J. M., Norris, L. M., and Halbert, M. L. *J. Nutrition 63:*425 (1957). The relationship of ascorbic acid to calcium and phosphorus metabolism has not been clear, in spite of several reports on the subject. The authors undertook a study on 12 healthy, women, college students to seek a clarification of the matter.

The study was divided into nine 5-day periods. During the first 3 periods, a planned basal diet was given. Sugar was allowed as desired during the second 3 periods, each basal meal for 6 subjects was supplemented with 65 Gm. of orange juice and for the other 6 subjects

with 25 mg. of ascorbic acid. These amounts were calculated to provide the National Research Council's recommended daily dietary allowance for vitamin C. The calcium and phosphorus content of the diet was calculated to be slightly below the minimal needs for maintenance in order to accentuate any effects of the supplements. During the last three periods, the subjects were again given the basal diet without supplementation of vitamin C.

Considerable variation among the subjects was noted in calcium and phosphorus absorption and retention. However, after statistical analysis of the resulting data, the authors concluded that calcium absorption and retention was significantly greater during the supplemented periods. There was a definite shift from a negative to a positive calcium balance during the supplemented period with a return to a negative calcium balance during the last period of the study. Although the group receiving the orange juice absorbed and retained a somewhat greater amount of calcium than did the group receiving ascorbic acid, the difference was not statistically significant.

Neither orange juice nor ascorbic acid, in the amounts given in this study, significantly influenced the utilization of phosphorus by these subjects.

Mass Inoculation With the Multiple Dose Jet Injector. Hingson, R. A., Davis, H. S., Bloomfield, R. A., and Brailey, R. F. *GP 15*:94 (May, 1957). The authors tabulated the results from 1,797 injections made with the Press-O-Jet, a multiple dose instrument for administering drugs subcutaneously under high pressure without the use of a hypodermic needle. The instrument consists of a pistol-shaped injector connected to a motor-driven hydraulic pump. A jet of solution at a velocity of about 700 miles per hour is forced through a micro orifice (0.003 to 0.005 inch). Developmental studies have shown that about 90 per cent of a 1 ml. jet injection traveled through the skin, subcutaneous fat and muscle sheath to distribute itself in the muscle about 0.75 to 1 inch below the skin surface.

With the Press-O-Jet, injections can be delivered as frequently as one every 4 to 6 seconds. In one instance a team of two physicians injected 200 patients within one hour. No sterilization is required between injections but the parts of the instrument coming in contact with the solution are sterilized prior to use. There is no danger of trans-

mitting blood-borne agents such as the virus of serum hepatitis since no part of the instrument penetrates the skin. There are, of course, no needles to clean or sharpen. Pain from injection was reported in only 13.9 per cent of the patients. The jet stream is so fine that it normally strikes very few nerve fibers. The important psychologic problem of fear of a hypodermic needle is eliminated.

Slight bleeding occurred in 25.8 per cent of the patients injected. This ranged from a tiny drop of blood to a fine trickle. Ecchymosis developed in a fairly high proportion of the patients injected, but it is of only temporary duration. However, should a patient or the operator move during the injection a superficial intradermal cut or zig-zag ecchymosis will be produced. Occasionally a patient will experience considerable momentary pain from the injection when a nerve fibril is hit directly by the jet stream.

The authors feel that this instrument has considerable potential usefulness in mass inoculation programs such as that for poliomyelitis vaccine.

The Sensitivity of the Human Eye to Hypo- and Hypertonic Solutions as Well as Solutions Not Isohydric. Trolle-Lassen, C. Presented before the International Pharmaceutical Federation, Sept. 14, 1957. The author presented the results, treated statistically, from a study of the effect on the human eye of solutions instilled therein. A group of thirty experimental subjects were given random instillations. The results were based upon the statistical evaluation of quantitative single observations.

It was found that the normal human eye had a fairly wide tolerance to ophthalmic solutions which were not isotonic. No irritation was observed from solutions with freezing point depressions from 0.41° C. to 0.77° C., corresponding to sodium chloride solutions between 0.7 and 1.4 per cent, respectively. Thus, the human eye has a greater tolerance toward hypertonic solutions than those which are hypotonic.

The author also reported that it was found that the sensitivity of the eye to hypo- and hypertonic solutions was independent of whether the solutions were prepared with substances capable of passing through the physiological membranes or with substances that do not possess this property. Solutions containing urea were used as an example of

the former and solutions containing sodium chloride as an example of the latter.

Studying the effect of hydrogen ion concentration, it was found that no significant irritation was produced by solutions varying in pH from 7.3 to 9.7. However, where the pH values of solutions were under 5.8 or over 11.4, irritation was nearly always produced.

The Disintegration of Tablets With Cellulose. Bequette, R. J., and Huyck, C. L. *Drug and Cosmetic Ind. 81*:166 (1957). The value of purified cellulose as compared with starch as a disintegrating agent in concentrations of 2, 5 and 10 per cent was investigated. Two formulations were compared, one containing lactose as representative of soluble substances and the other containing calcium gluconate as representative of insoluble substances. Both water and simulated gastric juice were used as the media in which to study the distintegration time, in accordance with the U. S. P. procedure. The size of the tablets and the compression pressure were kept constant.

Both the lactose and calcium gluconate tablets showed an increase in disintegration time as the percentage of starch increased. This was observed in both water and simulated gastric juice. Lactose tablets containing cellulose showed a shorter distintegrating time at a concentration of 5 per cent of the disintegrating agent than at either a 2 or 10 per cent concentration. Calcium gluconate tablets containing cellulose showed this same characteristic in simulated gastric juice but in water the disintegration time increased as the concentration of the distintegrating agent increased. At a concentration of 5 per cent of the disintegrating agent, cellulose gave a faster disintegration time than starch with both lactose and calcium gluconate tablets in both water and simulated gastric juice.

The authors concluded that cellulose was superior to starch as a disintegrating agent in the formulations tested. It also appeared to have possible superior value as a binding agent. Tablets made with cellulose were found to pull apart with a ripping action into several large pieces when tested for hardness on a Strong-Cobb hardness tester. Tablets made with starch snapped into many small pieces, when so tested.

BOOK REVIEWS

Veterinary Toxicology. By R. J. Garner. 415 pp. including index. Bailliere, Tindall and Cox, London (Williams & Wilkins, U. S. A.), 1957. $7.50.

It has been said, "Books are the ever-burning lamps of accumulated wisdom". Such a "lamp" is Garner's *Veterinary Toxicology*. With the ever-broadening drug and chemical armamentarium, hardly a day passes without the veterinary practitioner facing a toxicological problem.

Using Landers' Veterinary Toxicology as a framework, Garner has rewritten much of the original text, and brought the work up to date.

Part I is an introduction and provides general information on classification, general chemistry, metabolism, and mode of action of poisons. It also sets the pattern to be followed through the text, presenting data on absorption, symptoms, necropsy findings, and treatment.

The remaining seven parts treat of mineral or inorganic substances; organic compounds (drugs, pesticides, and miscellaneous); poisonous plants; radioactive materials; and an excellent chapter on toxicological analysis.

The book is indexed and extremely well documented. Workers in all branches of veterinary science and allied fields should find this text most valuable. It is recommended without reservation.

MARVIN J. SILVERMAN

Methoden der Organischen Chemie (Houben-Weyl). Volume 11, Part 1. Stickstoff-Verbindungen II. Herstellung von Aminen, I. Fourth Edition. Edited by Eugen Müller. xxxvii + 1178 pages. Georg Thieme Verlag, Stuttgart, 1957. DM 208 (approximately $48.50).

This volume of the renowned Houben-Weyl series deals with the preparation of amines. The presentation follows a classification of methods into the general types of preparative reactions that are employed, this classification providing the basis for division into chapters.

Eleven of the twelve chapters discuss the following methods of amine preparation, respectively: (1) Direct introduction of amino groups (15 pages); (2) preparation by exchange reactions (244 pages); (3) by addition reactions (75 pages); (4) by reduction (390 pages); (5) by condensation reactions (75 pages); (6) through use of organometallic compounds (22 pages); (7) by rearrangement reactions (101 pages); (8) by cleavage reactions (69 pages); (9) special methods of preparation (12 pages); (10) synthesis from other amines (22 pages); (11) preparative separation of primary, secondary, and tertiary amines (9 pages). A twelfth chapter (4 pages) deals with the properties and handling of ammonia. As in other volumes, the methods specify quantities of reactants and conditions of interaction.

The literature has been reviewed to 1956. The author index requires 78 pages, each of three columns, while the subject index occupies 63 pages.

This excellent work is another monumental contribution by the ten contributors and editors, as well as by the publisher, to the literature of chemistry.

ARTHUR OSOL

Die Chemie der Natürlichen Alkaloide (with special reference to their biogenesis). By Gertrude Woker. Second installment, pp. 499-732. Publisher: Ferdinand Enke Verlag, Stuttgart, Germany, 1956. Paperbound; DM 56. (Approx. $14.00).

The first part of this treatise was published in 1955. At that time, it was intended to be published in two parts; however, it became necessary to divide the monograph into three installments. This review covers the second installment.

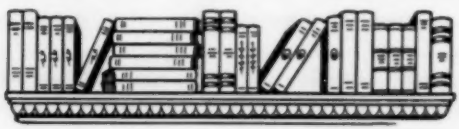
Again, as in Part I, emphasis is placed on the biogenesis of the naturally occurring alkaloids. The classification of these substances is arranged in accordance with their biogenetic interrelationship. In the first chapters, the alkaloids of Lobelia, Coca, and Ephedra are discussed from the standpoint of their chemistry, giving the constitutional characteristics as well as the synthesis. For the Coca alkaloids in particular, the discussions embrace also the sources and the phar-

macologic actions. A large folding table facilitates an easy survey of this group.

Other chapters deal with those alkaloids which are derivatives of tyrosine and oxytyrosines. Furthermore, biosynthetic relationships are shown between iosquinoline derivatives of oxytyramine, such as papaverine, berberine, and other closely related compounds.

There is a great amount of information presented in this installment. As it was in the first installment, the text is supplemented by excellent literature references. Part III, which will be published soon, will complete these valuable monographs.

ELSA EHRENSTEIN



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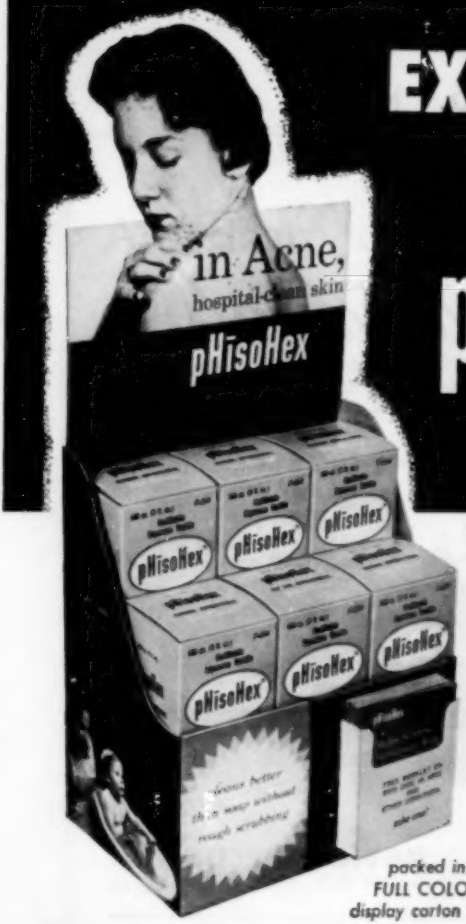

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